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EXAMINER	
HAWES, PILI ASABI	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,273	BRYNJELSEN ET AL.	
	Examiner	Art Unit	
	Pili A. Hawes	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-03-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt of the Information Disclosure Statement(s) filed 10-03-2005 is acknowledged. Claims 1-19 and 21-39 are pending in this action. Claims 1-19 and 21-39 are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 11, 21-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Desai et al. US 5916596.

Desai teaches a method of preparing nanoparticles of pharmacologically active agents by solvent evaporation technique from an oil-in-water emulsion prepared under conditions of high shear forces, such as sonication, high pressure homogenation, etc. Employing albumin as the biologically surface active molecule (col. 5, lines 43-52).

The method comprises the steps of homogenizing a mixture of organic phase and aqueous phase (col. 7, lines 40-50). The organic phase contains a pharmaceutically active ingredient and the aqueous phase contains a biocompatible polymer (col. 7, lines 40-50). The biocompatible polymer is a mixture of the pharmaceutically active agent and albumin (col.8, lines 6-7). This teaching anticipates

claims 7 and 11. The mixture is subjected to high shear conditions, such as sonication (col. 7, lines 40-50). This teaching anticipates claims 1-6.

Example 2 discloses a specific embodiment of the invention as claimed by applicant. The pharmaceutically active agent, paclitaxel is dissolved in a water immiscible solvent, methylene chloride (col. 17, lines 20-21). Methylene chloride is a solvent with a vapor pressure higher than water. This teaching anticipates claims 20-22. A solution of albumin is added to the organic phase and the mixture is homogenized (col. 17, lines 21-24) and a crude emulsion is formed col. 17, line 25). The crude emulsion is sonicated in a 40kHz sonicator cell (col. 17, lines 25-26). This teaching anticipates claims 5 and 23. The solvent is evaporated and the particles are harvested with a particle size of 350-420 nm (col. 17, lines 26-31). The example also discloses that the particles can be reconstituted to the original dispersion by adding water (col. 17, lines 35-36). This teaching anticipated claims 25-29.

The pharmaceutically active ingredients recited in claim 24 are anticipated by teaching of pharmaceutical active ingredients suitable for the process taught by Desai. The specific example of paclitaxel as the active ingredient anticipates claim 24 because paclitaxel is an antineoplastic.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 and 21-39 rejected under 35 U.S.C. 103(a) as being unpatentable over Parikh et al. US 5922355 in view of Chagnon et al. US 5389377.

Parikh discloses a method of preparing submicronized particles of poorly water soluble pharmaceutically active agents comprising reducing the particle size through sonication, homogenization, milling, micro fluidization and precipitation or recrystallization and precipitation of the compound using antisolvent and solvent precipitation techniques (col. 10, lines 23-29). The steps of the method comprise mixing the water insoluble pharmaceutically active ingredient, a phospholipid, with at least one

nonionic, anionic, or cationic surfactant (col. 10, lines 30-34). Suitable surface active modifiers used in the invention are listed in column 3, lines 6-30).

Example 1 discloses a specific embodiment Parikh's invention, preparing microparticles of cyclosporine. Cyclosporine is added to mannitol (col. 4, lines 44-46). Mannitol is an organic compound and is an alcohol. To the organic phase is added egg phosphatidylcholine and a surface-active agent, Tween (col. 4, lines 44-46). The mixture is homogenized and sonicated (col. 4, lines 50-56). A suspension of the particles was made in water (col. 5, 2-3). The particles sizes of the particles were in the range 337-361 nm (col. 5, lines 10-22). Parikh lists types of water insoluble pharmaceutical compounds that would be suitable for this invention (col. 2, lines 52-64). The number weighted particle size range is 63-76 nm (col. 5, lines 20-22).

Although the reference does not specifically teach what the solvent and anti-solvent are for the method of preparing submicronized particles, it would be obvious to one of ordinary skill in the art that a poorly water soluble compound would be soluble in an organic solvent, and an anti-solvent of an organic solvent would be an aqueous solvent. Sonication as a method of solvent removal is well known in the art.

Chagnon teaches a method of preparing liposomes comprising a sonication step which removes organic solvents from its anti-solvent, water (col. 7, lines 65-68).

In view of the anti-solvent/ solvent method of precipitation taught by Parikh and the teaching that sonication is a good method for removing organic solvents to obtain microparticles or liposomes suspended in water, one of ordinary skill in the art would be motivated to combine the two reference teachings to prepare submicronized particles of

poorly water soluble pharmaceutically active compounds. One of ordinary skill in the art would be motivated to use sonication as opposed to other methods of solvent removal because sonication provides a gentler way of removing the solvent, and would reduce the potential for loss of product or damage to the product using other conventional methods of solvent removal, such as high temperature or reduced pressure evaporation.

Claims 1-7, 11, 21-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. US 5916596.

Desai teaches a method of preparing nanoparticles of pharmacologically active agents by solvent evaporation technique from an oil-in-water emulsion prepared under conditions of high shear forces, such as sonication, high pressure homogenation, etc. Employing albumin as the biologically surface active molecule (col. 5, lines 43-52).

The method comprises the steps of homogenizing a mixture of organic phase and aqueous phase (col. 7, lines 40-50). The organic phase contains a pharmaceutically active ingredient and the aqueous phase contains a biocompatible polymer (col. 7, lines 40-50). The biocompatible polymer is a mixture of the pharmaceutically active agent and albumin (col.8, lines 6-7). This teaching anticipates claims 7 and 11. The mixture is subjected to high shear conditions, such as sonication (col. 7, lines 40-50). This teaching anticipates claims 1-6.

Example 2 discloses a specific embodiment of the invention as claimed by applicant. The pharmaceutically active agent, paclitaxel is dissolved in a water immiscible solvent, methylene chloride (col. 17, lines 20-21). Methylene chloride is a

solvent with a vapor pressure higher than water. This teaching anticipates claims 20-22. A solution of albumin is added to the organic phase and the mixture is homogenized (col. 17, lines 21-24) and a crude emulsion is formed col. 17, line 25). The crude emulsion is sonicated in a 40kHz sonicator cell (col. 17, lines 25-26). This teaching anticipates claims 5 and 23. The solvent is evaporated and the particles are harvested with a particle size of 350-420 nm (col. 17, lines 26-31). The example also discloses that the particles can be reconstituted to the original dispersion by adding water (col. 17, lines 35-36). This teaching anticipated claims 25-29.

The pharmaceutically active ingredients recited in claim 24 are anticipated by teaching of pharmaceutical active ingredients suitable for the process taught by Desai. The specific example of paclitaxel as the active ingredient anticipates claim 24 because paclitaxel is an antineoplastic.

It is well known in the art to use sonication as an organic solvent removal method. It would be obvious to one of ordinary skill in the art that the solvent could be removed without a further evaporation step because Desai teaches that the step is optional (col. 7, lines 52-55). One of ordinary skill in the art would be motivated to use sonication as opposed to other methods of solvent removal because sonication provides a gentler way of removing the solvent, and would reduce the potential for loss of product or damage to the product using other conventional methods of solvent removal, such as high temperature or reduced pressure evaporation.

Response to Arguments

Applicant's arguments filed 10-05-2005 have been fully considered but they are not persuasive. Applicants argue Desai does not teach evaporation of the organic solvent using sonication as in claim1. The Examiner points out that claim 1 states that the sonicating system evaporates a portion of the water immiscible organic phase, however the claims does not recite a particular percentage or amount of organic solvent removed by the sonication process. As the reference does teach sonication of the emulsion, and **optionally** further removing organic solvent with the rotoevaporator, it is the position of the Examiner that the conditions of the instant claims are met by the instant reference. It is well known in the art the sonication can be used to evaporate organic solvents. It is the Examiners position that "a portion" of the organic solvent would have been removed by the method taught by Desai. Applicants have not further defined what is meant by "a portion" of the solvent that is being removed. Thus the reference is still anticipatory and the rejection is maintained.

Conclusion

Claims 1-19 and 21-39 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pili A. Hawes whose telephone number is 571-272-8512. The examiner can normally be reached on 8-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

P.A. Hawes
Examiner-1615

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